REMARKS

The invention relates to a method for predicting a prognosis in a patient with an acute coronary syndrome. The method involves testing a body fluid from the patient for two markers using an antibody-based assay (*e.g.*, an immunoassay). One marker is cardiac Troponin-T or cardiac Troponin-I and the second marker is BNP, NT-proBNP or pro-BNP. Binding of the antibodies to the markers in the body fluid sample provides a mechanism to determine a prognosis for the patient.

Claims 23-38 are currently pending in the application. No amendments to the claims are made in this submission.

Applicants respectfully request reconsideration of the claimed invention in view of the foregoing amendments and the following remarks.

Non-Art Based Remarks

1. Continued Examination

Regarding the request for continued examination filed by Applicants in this application, the Office Action states that "the finality of the previous Office action has been withdrawn." To ensure a correct record, Applicants note that, prior to the request for continued examination, a notice of allowance had been issued. Applicants filed the request for continued examination to introduce an IDS listing material from an interference that was concluded in favor of the present application.

2. Election/Restriction

In the Office Action, the Examiner provides a formal election of species requirement following Applicants telephonic election. Applicants confirm the election of (1) a method of predicting a mortality rate as a prognosis, and (2) the troponins as a first marker. Claims 23-28, 32-34, and 38 read upon the elected species.

3. Rejection of claims 23-28, 32-34, and 38 under 35 U.S.C. § 112, second paragraph

Applicants respectfully traverse the rejection of claims 23-28, 32-34, and 38 under 35 U.S.C. § 112, second paragraph, as allegedly failing to comply with the definiteness requirement.

When determining definiteness, the proper standard to be applied is "whether one skilled in the art would understand the bounds of the claim when read in the light of the specification." *Credle v. Bond*, 30 USPQ2d 1911, 1919 (Fed. Cir. 1994). Recognizing that the English language is not always precise, the settled law has established that the essential inquiry in a definiteness analysis is whether the claims set out and circumscribe the claimed subject matter with reasonable particularity. *See, e.g.,* MPEP § 2173.02; *see also, Miles Laboratories, Inc. v. Shandon, Inc.*, 27 USPQ2d 1123, 1127 (Fed. Cir. 1993) ("If the claims read in the light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more.") (emphasis added). Definiteness is not analyzed in a vacuum, but in light of the content of the specification, and with the knowledge available to the skilled artisan.

The rejection of claims 23, 25, 27, 33 and their dependent claims, is premised on an allegation that "it is not clear how cardiac mortality rate is predicted," and that the claims "[do] not indicate how prediction is made. Would the mere presence of a marker, i.e., any binding detection, indicate mortality rate? What would the rate be? Would all markers have to be present? Or would there just be a comparison to a control? What kind of comparison? What increased level of marker(s) must there be?"

As an initial matter, Applicants note that the language to which the Examiner objects in claims 23, 25, and 27 (claim 33 contains slightly different language, but is rejected solely for the same reasons as claims 23, 25, and 27) has been present in the claims throughout the period during which the present application was allowed, was prosecuted through an interference proceeding, and finally received a formal notice of allowance. Thus, the introduction of the definiteness rejection at this stage of prosecution is somewhat surprising.

Regarding the merits of the rejection, Applicants respectfully submit that the Examiner's allegations, and the questions posed, are not indicative of indefiniteness. Rather, the Examiner's comments indicate a failure to consider either the knowledge available to the skilled artisan or the content of the specification. Moreover, the fact that the claims embrace different ways in which the immunoassay results may be used to assign a mortality rate to a patient is indicative of breadth. Such breadth does not equate to a failure to meet the definiteness requirement. *See, e.g.*,

MPEP § 2173.04 ("Breadth is not Indefiniteness"). When properly considered, the present claims comply with the definiteness requirement.

The rejected claims refer to the use of at least two polypeptide markers, one of which is BNP, NT-proBNP, or pro-BNP, and the other of which is cardiac troponin I, cardiac troponin T, CK-MB, or C-reactive protein, in methods for assigning a prognosis (*e.g.*, a likelihood of death) to a patient. These methods comprise performing immunoassays for the two markers on a sample from the patient, where binding of the markers to their respective antibodies (that is, the immunoassay result for the two markers) is determined. The assay results obtained are used to assign the prognosis of interest to the subject.

Various methods for assigning a prognosis based on such assay results are well known in the art. Consider, for example, Antman *et al., N. Engl. J. Med.* 335: 1342-49, 1996, cited by the Examiner in the Office Action. In Figure 3 (page 1347), mortality rates are determined by separating measured troponin I levels into 6 "bins," where the lowest bin (0 to < 0.4 ng/mL) has a mortality rate of 1%, and the highest ($\geq$9.0 ng/mL) has a mortality rate of 7.5%. Thus, depending on the particular bin a patient might fall into, a different mortality rate could be assigned to the patient.

In contrast, Richards *et al., Heart* 81: 114-20, 1999, also cited by the Examiner in the Office Action, uses a single value, the median BNP value of 27 pmol/L, to determine a mortality rate, stating on page 117, left column, that the measured level in a patient, relative to this median value "discrminiated between patients destined or not to die." Thus, depending on which side of this median value a patient might fall, a different mortality rate could be assigned to the patient.

In Newby *et al.*, *Circulation* 103: 1832-37, 2001, also cited by the Examiner in the Office Action, multiple markers are combined in the following fashion to assign a mortality rate: any one marker in a panel of two or three markers that is above the upper limit of normal for that marker triggers a positive result. *See* page 1833, left column, section entitled "Cardiac Markers". Thus, if one, two, or three markers are above the upper level measured in a normal population, a different mortality rate could be assigned to the patient.

As indicated in these publications, the skilled artisan understands that the methods by which assay results may be used to assign a prognosis to a patient are varied. As such, the precise

methods to be used are best left to the discretion of the skilled artisan, depending upon the level of sensitivity and specificity desired from the method. Thus, the mere presence of a marker might be used to indicate a mortality rate. Alternatively, particular bins might be used. In another alternative, a median value in diseased subjects might be used as a threshold. In yet another alternative, a level above that seen in a normal population might be used as a threshold. And, as seen in Newby, all markers need not be present to practice the claimed invention using multiple markers, as long as the multiple markers are measured, and the multiple assay results are used in assigning a prognosis.

With regard to how particular values of the markers might relate to a particular mortality rate, the skilled artisan further understands that the particular value of a marker in a subject, and thus how that level relates to mortality, may likely be dependent upon the particular assay employed by the artisan. In the case of cardiac troponin I, for example, it has been reported in the literature that measurements using different commercial troponin I assays on identical specimens may differ in measured concentration by 100-fold. *See, e.g.*, Christenson *et al.*, "Standardization of Cardiac Troponin I Assays: Round Robin of Ten Candidate Reference Materials," *Clin. Chem.* 47: 431-37 (2001). Thus, a troponin I level from one assay might indicate one mortality rate, while the same level from a different assay would indicate an entirely different mortality rate. Determining the relationship of one or more marker levels to mortality is a straightforward determination performed simply by assaying the marker(s) in an appropriate subject population, using the assays selected by the artisan. As indicated from the troponin I example discussed above, such determinations are routine in the art.

Consistent with the foregoing, the present specification notes on page 5, last full paragraph, that a prognosis is often determined by examining one or more prognostic indicators. On page 6, first full paragraph, the present specification teaches that correlating marker levels to a particular outcome is often performed by comparing a level in a patient to levels in a subject population exhibiting a particular characteristic. In the next three paragraphs, the present specification indicates that this might be performed by merely checking the presence or absence of a marker level. Alternatively, a threshold level or a nomogram (such as might be represented by a binning strategy) might be used.

Again, the fact that the present claims are sufficiently broad to capture these various methods for relating assay results to a prognosis does not equate to a failure to meet the definiteness requirement, as breadth is not indefiniteness. MPEP § 2173.04. Rather, all that is required is that, when the claims are read in the light of the specification, the skilled artisan is reasonably apprised of the scope of the invention. Applicants respectfully submit that, consistent with the previous allowance in this very application of such claim language, the present claims meet this definiteness standard.

Because the claims reasonably apprise the artisan of the scope of the invention, and because 35 U.S.C. § 112, second paragraph demands no more, Applicant requests that the rejection of claims 23-28, 32-34, and 38 be reconsidered and withdrawn.

4. Rejection of claims 23-28, 32-34, and 38 under 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 23-28, 32-34, and 38 under 35 U.S.C. § 103(a) as being unpatentable over Newby *et al.*, *Circulation* 103: 1832-37, 2001, in view of Antman *et al., N. Engl. J. Med.* 335: 1342-49, 1996, and Richards et al., Heart 81: 114-120, 1999.

The effective date cited by the Examiner for the primary Newby *et al.* publication is April 10, 1002 (three days prior to the filing date of the present application). Thus, Newby *et al.* is citable as prior art only under 35 U.S.C. § 102(a). As such, a declaration under 37 C.F.R. § 1.131 may be used to antedate the cited publication, thereby removing it as citable prior art. Applicants submit herewith such a declaration executed by all of the inventors named in the present application.

In addition, selected pages from a draft version of the present patent application are provided as documentary evidence in support of the declaration. As discussed in paragraph 9 of the declaration, this draft version of the present patent application was prepared prior to the publication date of Newby *et al.*

As demonstrated in paragraph 9 of the declaration, the draft version of the present patent application shows that the present inventors had reduced to practice the present invention prior to the effective date of Newby *et al.* The following table applies an example described in the draft

application to present claim 23. Application to independent claims 25, 27, and 33 is essentially identical.

Claim	Citation to Draft Application
23. A method for predicting cardiac mortality rate in a patient with an acute coronary syndrome, comprising:	blood specimens were collected from a subpopulation of 2,525 patients enrolled in the OPUS-TIMI 16 study that were diagnosed with an acute coronary syndrome (page 13, lines 1-10)
drawing a sample of a body fluid from said patient,	See above.
contacting said sample with a first antibody that specifically binds to a first marker selected from the group consisting of cardiac Troponin-T and cardiac Troponin-I;	cardiac troponin I was measured using standard immunoassay techniques (page 13, line 12)
contacting said sample with a second antibody that specifically binds to a second marker selected from the group consisting of BNP , NT-proBNP, and pro-BNP;	BNP was measured using standard immunoassay techniques (page 13, line 12)
providing means for determining binding between each of said respective markers and each of said respective antibodies, whereby said binding provides a means for determining cardiac mortality rate.	The results of these assays were combined to produce mortality rates (presented as adjusted 10-month mortality in subjects stratified using 100 pg/mL cardiac troponin as a threshold. (Figs. 2 and 3)

While the reduction to practice of the claimed invention as demonstrated above should be sufficient to overcome the present rejection, Applicants further note that the declaration also shows conception of the claimed invention, which, coupled with diligence from just prior to the effective date of the primary Newby *et al.* publication, is also sufficient to overcome the present rejection. Applicants respectfully submit that revising and filing the present application within three days of the effective date of the primary Newby *et al.* publication shows sufficient

diligence. In addition to the support for conception provided in the foregoing table, additional support may be found in the specification as follows.

Claim	**Citation to Draft Application**
23. A method for predicting cardiac mortality rate in a patient with an acute coronary syndrome, comprising:	the draft application describes the invention as being "determining a prognosis in a patient having an acute coronary syndrome. One such prognosis is the risk of death (pages 3 and 4)
drawing a sample of a body fluid from said patient,	the draft application provides that body fluids are appropriate samples (page 7)
contacting said sample with a first antibody that specifically binds to a first marker selected from the group consisting of cardiac Troponin-T and cardiac Troponin-I;	the draft application describes combining BNP measurements with cardiac troponin measurements (page 6), and the use of antibody binding assays (immunoassays) (page 12) for measuring markers, the results of which are used for determining a prognosis.
contacting said sample with a second antibody that specifically binds to a second marker selected from the group consisting of BNP , NT-proBNP, and pro-BNP;	See above.
providing means for determining binding between each of said respective markers and each of said respective antibodies, whereby said binding provides a means for determining cardiac mortality rate.	See above.

Applicants respectfully submit that the declaration under 37 C.F.R. § 1.131 and the accompanying documentary evidence removes the primary Newby *et al.* publication as citable prior art. Accordingly, Applicants request that the rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

CONCLUSION

Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the

Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

Date 05/11/2006

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